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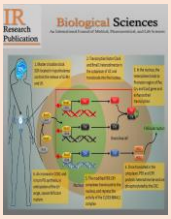

Micro-needles as an effective drug delivery system and associated patents in pharmaceutical field: A Review

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ABSTRACT

Microneedles (MNs) are the most interesting and minimally invasive technique in pharmaceutical drug delivery systems. Recently researchers have concluded that MNs can be prominent future methods. Depending on the unique properties of MNs, they can be used widely in drug delivery systems. This delivery method has improved drug delivery avoiding many hurdles that were linked with the conventional system. The principal mechanism involved is temporarily damaging the skin layer; hence micron-size pores are created, which help the drug to reach the targeted site without any complications. The popularity of MNs in pharmaceutical and biomedical research is growing exponentially as it offers easy delivery of bio-actives to the specific site with minimal invasion. Several numbers of molecules are delivering via MNs, such as hormones, vaccines, and peptides. In this review, the efficiency of Micro-needle, their fabrication materials, as drug delivery carriers, and various associated patents are discussed.

Introduction

Several procedures are there to deliver bio-actives in the specific portion of the body, but among this oral drug delivery system has been widely received because of having an easy mode of administration and better patient compliance [1]. But sometimes, this oral drug administration is unable to cross some specific limitations from our physiological system, and thus the importance of other delivery systems has become into consideration. For example, transdermal drug delivery system (TDDS) where the drugs are administered via external stratum corneum (SC) [2]. This outmost layer is the primary blockade for topically administered formulations. It permits the drug(s) only with (molecular weight < 500 Da) and having lipophilic nature and low melting point in nature. Hence, to conquer the complication from the last decades, researchers are

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giving an eye to MNs technology which can easily reach the dermis layer with eliciting minimum pain to the patient [3]. MNs systems have become a popular option due to offering many advantages over conventional drug delivery systems [4], [5], such as transferring drug molecules by skin barriers without causing any permanent tissue damage and pain. Gerstel and Place firstly conceived this technology for the passage of bio-actives in 1971. At first, MNs were used as a puncturing tool, but later in the 1990s it was used as a drug delivery carrier. It provides a sooner healing rate compared to conventional procedures by bypassing the first-pass metabolism of the therapeutics and hence can attain safe and effective pharmacokinetics and pharmaco-dynamics response. Even though MNs can deliver high molecular weight components in a controlled manner at the targeted site, which is widely accepted in pharmaceutical drug applications. MNs produce micron-sized channels for the deliverance of therapeutics. Generally, the MNs can easily reach the dermis layer without touching the nerves. They are 100 μm lengthy, 1–50 μm wide at the tip, and about 50 to 300 μm at the base [6]. Micro-needles are fabricated from a wide diversity of components, including metal, polymer, glass, silicone, and hydrogel. Though having many applications in the pharmaceutical field but in targeted delivery, DNA, protein delivery, it is necessary to explore more [7]. In **Figure 1** various drug delivery system along with Micro-needles (MNs) has been described.

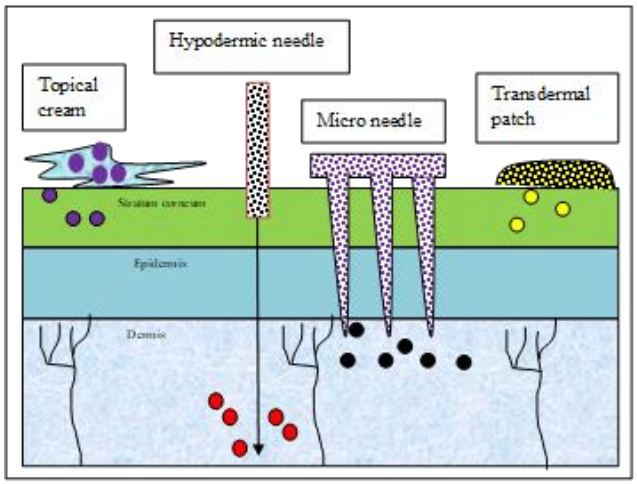

Figure 1. Description: Comparison between various drug delivery systems

Fabrication of MNs

Different types of components are used to prepare MNs. It uses polymeric substances such as natural, biodegradable, non-biodegradable, and metals [8], [9]. The basic requirements for polymers, metals, and metalloids are biocompatibility and good mechanical properties [10]. It must provide chemical resistance and show important physical characters that can make MNs a multipurpose material for the pharmaceutical field [11]. Especially the polymeric MNs or dissolvable MNs, the material must control the release of drug (like controlled or in a sustained manner) [12]. As an alternative, MNs that are made up of polymeric material must follow the prerequisite of MNs [13]. The first MN was developed from silicon in the 1990s. Generally, the foremost used metals are stainless steel and titanium, even though palladium, nickel can also be applied. Metals offer good mechanical strength and are biocompatible. They are strong enough to evade breaking associated problems inside the body, therefore more appropriate than silicon-based MNs. Titanium is a better substitute for stainless steel [14]. Alumina is mostly applied because of having good chemical-resistant properties. It produces stable oxide due to having strong ionic and covalent bonds between Al and O atoms [15]. Other ceramics utilized such as calcium sulfate dehydrate and calcium phosphate dehydrate. In recent years an organically modified ceramic called Ormocer® has been used. It is a three-dimensional cross-linked copolymer [16]. A broad variety of polymers are used such as poly-methyl methacrylate, poly-lactic acid, poly-lactic-co-glycolic acid, cyclic-olefin copolymer, poly vinyl-pyrrolidone, are also used to develop micro-needles [17], [18], [19], [20], [21]. Maltose is generally used sugars, and other types of sugars are including mannitol, sucrose, xylitol, and galactose, may also be used. Mould is prepared by using carbohydrate slurries with the help of silicon or metal templates. The drug-encapsulated carbohydrate mixture is cast into the molds to produce MNs [22]. **Table 1** described about various casting methods of MNs development [23], [24], [25].

Method of drug delivery

Topical delivery of bio-actives through skin via diffusion process. Micro-needle provisionally damages the skin tissue. The device is developed by arranging hundreds of MNs in arrays on a tiny patch to transport enough bio-active to show the required therapeutic response. It crosses the stratum corneum, thus bypassing the layer easily. The drug goes straight to the desired place and into the systemic circulation and gives a therapeutic action [26], [27]. The mechanism of drug delivery through MNs is depicted in **Figure 2**.

Types of MNs

Various types of MNs are investigated to use in drug

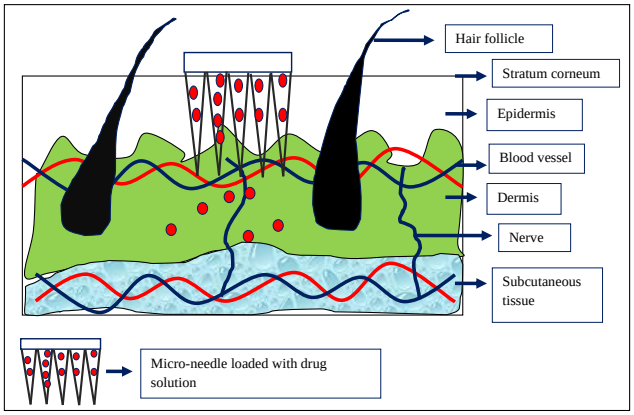

Figure 2. Micro needle device with drug solution then device inserted into the skin thus temporary mechanical disruption of the skin then releasing the drug in the epidermis and finally transport of drug to the site of action.

delivery systems, including solid, coated, dissolving, hollow, and hydrogel MNs. Such MNs with their drug release mechanism is described in **Figure 3**, where each of them has its own mechanism to transport the drug into the epidermis. Few of them are applied to create pores in the stratum corneum, some are pre-coated with the drug solution on to their surface, and some are prefilled with drug solution [28], [29].

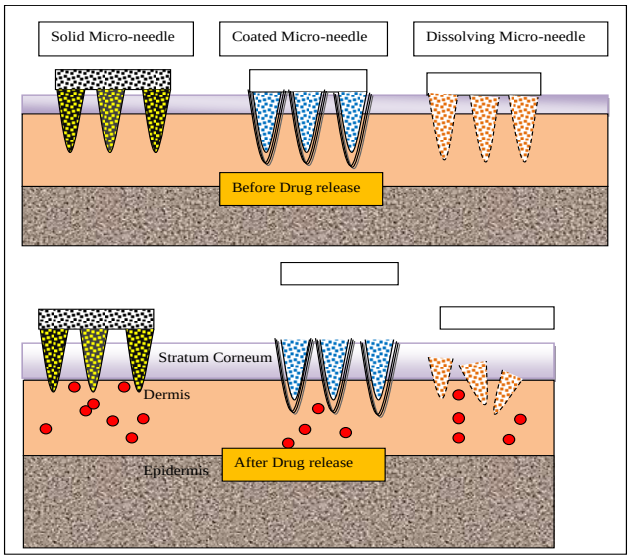

Figure 3. Description: Different types of Micro-needles and drug release mechanism

Methods of delivering drug

Different options are used to transport the drug into the epidermis layer. One mechanism is to make holes, and then a drug-holding patch is placed in the hole, which involves straight transportation of therapeutics into the target site; an electric field is applied to get a better result. The second mechanism is to coat the MN drug-containing solvent that is inserted into the skin where the drug gets dissolved. The third method is to immerse the MNs into the drug dissolving solution and then rub the needles on the skin. Another approach is to encapsulate the drug into a biodegradable polymer and develop the MNs. In the case of the hollow MN, the drug reached solution is filled into the hollow space [30], [31]. Drug-encapsulated biodegradable MNs have been broadly applied for the active delivery of drug moieties [32].

Application of MNs in drug delivery system

Various research studies are going on to check the efficacy of MNs in various parts of the pharmaceutical and biomedical fields. This system offers excellent drug, protein, and peptide encapsulation for their controlled or sustained release in the specific site. Not only in transdermal drug delivery but also act as a tremendous mechanism for drug delivery via nail, nasal, ocular, and ear. A variety of pharmaceutical applications of MNs have been discussed below.

Oligonucleotide delivery

The major challenge of this DNA or RNA-based molecule is the intracellular site of action; hence, several methods are used to improve the movement of the molecule. For example, 20-merphosphorothioated oligo-deoxynucleotide was delivered by using the MNs technique. Solid MNs are basically used to deliver oligonucleotide by creating the pore with patch approach. It was found that more amount of drug is reaching at the required site as compared to the intact skin. By applying the iontophoresis mechanism with the MNs technique provided greater results than iontophoresis alone [33], [34].

Vaccine therapy

This biological preparation gives acquired immunity to a specific disease. Basically, the vaccine boosts the immune system and offers defence against future infection. MNs method provided effective results in vaccine therapy [35]. For example, DNA vaccine was delivered by utilizing MNs. The immune response showed far better than normal injections. Even a MN-based influenza vaccine was also made to administer [36], [37]. A lower dose is required when the bio-active moiety is given via hollow MNs in comparison with intramuscular injection. Anthrax and rabies vaccine was given through hollow MN. Ogai and co-workers developed hollow MNs by using poly-glycolic acid to improve the efficacy by the intradermal route. Dissolving MNs were also tested for intradermal vaccination [38]. Zhu et al. conducted the stability of a vaccine-loaded MN and

Table 1. Different casting methods for developing Micro-needles

Type of MNs	Method of fabrication
Silicon MNs	Micro-electromechanical systems (MEMS) techniques, thin-film deposition on a substrate, chemical vapor deposition on a substrate, Silicon dry-etching process, Isotropic etching, etc.
Metal MNs	Three-dimensional laser ablation, laser cutting (stainless less), metal electroplating methods (palladium), wet etching photochemical etching (titanium), etc.
Ceramic MNs	Ceramic micro molding and sintering lithography, etc.
Coated MNs	Dipping or spraying, layer-by-layer (LbL) coating techniques
Hollow MNs	Deep reactive ion etching of silicon, deep X-ray photolithography, wet chemical etching, and micro-fabrication, Integrated lithographic molding technique, etc.
Dissolving MNs	Micro-molding
Polymeric MNs	Photolithography, micro molding, casting, hot embossing, injection molding, investment molding, etc.

concluded that trehalose resulted in considerably higher stability rather than sucrose and that 80% of the early antigenicity was retained under stress conditions (60 °C/3 months) [39]. To further boost immunogenicity, an immune-modulatory cytokine, granulocyte-macrophage colony-stimulating factor (GM-CSF), was utilized to MNs to persuade a long-lived antibody action. For stable and effective transport of GM-CSF, a microneedle using trehalose, CMC, or gelatine was used [40]. A third-generation hepatitis vaccine MN that contains 15% trehalose showed enhanced stability rather than conventional liquid formulations, including stability for 1 week at 40 °C [41].

Peptide delivery

When peptides are taken orally, they get degraded by enzymes. To avoid this limitation, transdermal delivery is applied, but a very less amount of peptide was successful in crossing the skin. Thus, MNs based peptide is now used to avoid such challenges by the skin barriers. For example, a desmopressin-based MN technique is used to deliver desmopressin safely and efficiently. Cyclosporin A, another cyclic peptide, was delivered using dissolving MNs having the dimension of 600 μm in length and 250 μm wide [42].

Hormone delivery

Some peptide hormone, such as insulin, was given via MN and showed decreased blood glucose levels than normal injections [43]. Li et al. cast solid MNs and checked the effect on blood glucose levels in diabetic mice. The outcome confirmed a decrease in blood glucose level to 29% of the initial value after 5 hours that concluded that enhanced permeability of insulin via MNs [44]. Ye and co-workers also investigated MNs with pancreatic β-cell.

Ocular delivery

Posterior segment symptoms can be minimized with the help of a targeted drug delivery system. The Iontophoresis method was used to transport the nanoparticles into the suprachoroidal place, whereas without iontophoresis, the particles were found to be at the injection site. In combination with MN (>30%) of nanoparticles moved successfully to the targeted site of action [45]. Singh et al. developed quick-dissolving polymeric MNs for intraocular drug delivery. MNs were cast by using PVP polymer having different molecular weights such as fluorescein, sodium, and fluorescein isothiocyanate–dextrans (MW of 70 kDa and 150 kDa). The system resulted in a fast dissolution rate, and in vitro testing of MNs concluded the permeability of the macromolecule. Furthermore, the confocal descriptions concluded that macromolecules formed depots within the tissues that result in sustained release of drugs [46]. Than et al. concluded self-implantable double-layered micro drug reservoirs for proficient and restricted ocular drug delivery. MNs can also be used as micro reservoirs to deliver the drug in a controlled manner. The study stated that antiangiogenic monoclonal antibody (DC101) could be transported by using an eye patch which results in ~ 90% reduction of the neovascular area and also offers synergistic effects [47]. In 2016, Khandan and his team had been aperture MNs for ocular drug delivery. The potential of MNs is enhanced up to 5-fold [48]. Additionally, Kim and co-workers also reported MNs for site-specific antiglaucoma drug delivery [49].

MNs as a sensor

Recently a rising interest is seeing in the use of transdermal MN-based electrodes in favor of molecular-based bio-sensing and drug delivery [50]. As examples of MN-based biosensors have

been explored for continuous screening of metabolic markers like glucose and lactate and organophosphate nerve agents [51]. These sensors can cross the SC only and therefore do not cause pain or draw blood, as they do not reach the nerve endings and capillary blood vessels in the dermis. The sensors offer less invasive for drug or metabolite controlling [52]. Gowers et al. cast an MN-based sensor for continuous monitoring of β-lactam antibiotic concentrations in vivo. This sensor is coated with a pH-dependent iridium oxide layer, indicating the alteration of pH [53]. Another MNs based array was described that regulates glucose level. Thus, MNs reduces several manifestations to check the glucose level in comparison with other devices [54]. Other MNs (nitrogen-based ultra-nanocrystalline diamond) have been developed for sensing, as stated by Skoog et al. This nitrogen-based sensor can sense electrochemical signals of dopamine and uric acid [55]. The MN-based biosensor was also used in electrical recognition, described by Keum et al., a promising platform for detecting cancer [56].

MNs for drug delivery to the brain

Several methods are already explored by which the BBB can be crossed to treat brain-associated diseases by using nanocarrier. Recently the MNs as a non-invasive technique are found to be more efficient in brain drug delivery. Kearney et al. investigated the donepezil hydrochloride entrapped MN patches to treat Alzheimer's diseases [57]. One more study was conducted about silicon-based MNs to transport the drug into the deep brain. In this regard, a silicon-based MN array was cast to recognize interlink as well as neuronal functions [58].

Delivery of proteins

Bovine serum albumin (BSA) is basically used as a model protein that is transported via microneedles [59]. Cheung et al. utilized the focused ion beam technique (FIB) to develop MNs and showed enhancement in the absorption of BSA by applying 'poke and patch technique. The study concluded that the absorption of BSA through the skin is only feasible while using a pre-perforation of the stratum corneum by using MNs to create a necessary passage for the protein [60]. Mönkäre et al. entrapped monoclonal IgG (10% w/w) in dissolving HA MNA. This procedure successfully passed the epidermis of ex vivo human skin, and after 10 min, the MNA was almost entirely dissolved [61].

Cosmetics

Having smooth and less invasive action onto the skin surface, MNs are widely used to treat different skin-associated problems such as seborrheic keratosis, scars, anti-aging, wrinkles, etc. 'Dermaroller' is one of the accepted examples of MNs based instrument. Machekposhti et al. developed MNs by utilizing PVP and methacrylic acid encapsulated with TXA. These MNs showed adequate properties for the management of melasma [62]. Hibrobe et al. prepared an ATRA-entrapped MN patch (ATRA-MNs) for permeability enhancement of ATRA and MN patch loaded with retinoic acid. ATRA-MNs are used on the lesion site once per week for up to 4 weeks [63]. Triamcinolone acetonide-loaded MNs are also used reported by Chandrashekar et al. [64]. Administration of corticosteroids by using MNs showed enhanced blood supply to hair follicles [65]. Enhanced delivery of melanostatin, rigin, and pal-KTTKS was also investigated with the MNs [66]. Jingtong Pan et al. in 2018 concluded that dissolving MNs of STAT3 siRNA PEI complex has decreased the development of melanoma very efficiently and dose vulnerably by modifying the STAT3 gene. Therefore, the study concluded that dissolving MNs associated with STAT3 siRNA can be a promising way to treat skin melanoma with reduced side effects [67].

MNs in transdermal drug delivery

Owing to the drawbacks of the oral and traditional path of management, the transdermal patch has been broadly commonplace because of imperative characteristics that assist in attaining the required plasma concentration on the target site for an extended duration [68]. Thus, MNs are taken into consideration as a more promising tool for TDDS as micro-channels created via them allow the smooth and painless transport of therapeutics compared to that of hypodermic needles [69]. Wu et al. Fabricated sumatriptan succinate (SS)-loaded MN arrays from sodium hyaluronate to enhance their healing efficacy for transdermal shipping. Ramadan et al. Advanced polymeric lamivudine (LAM) loaded NPs for transdermal delivery thru passive diffusion and MN-mediated delivery was similarly investigated for long-term stability and penetration enhancement [70]. Yu et al. mentioned a glucose-responsive insulin transport tool by the usage of a painless MN patch coined as a 'smart insulin patch' that carries glucose-responsive insulin and glucose oxidase (GOx) loaded vesicles. This clever and new insulin MN patch efficiently regulated blood glucose of chemically induced diabetes type 1 within the mouse version [71]. Zhao et al. defined MNs as a potential method in transdermal delivery and application within the management of psoriasis [72]. Niu et al. found that intradermal delivery with the aid of a hollow MN array creates a sustained launch depot within the pores and skin and might create a

burst transit through draining lymph nodes [73]. Researchers have evolved MNPs to enhance the MTX remedy efficacy for psoriasis and decreased the facet effects because of MNs [74], [75]. Ajay K. Banga and teammates' works have stated that after MTX is carried out underneath MNP pre-treated skin, the delivery of MTX is more powerful than with significant strategies [76]. Korkmaz et al. advanced a type of DMN loaded with anti-TNF-a Ab in the pointers of the needles and determined that this method validated powerful delivery efficacy and anti-inflammation function in BLAB/c mice with psoriatic lesions caused by using imiquimod [77].

MNs in Cancer therapy

Self-degradable Microneedles had been investigated for cancer treatment by using supplying over anti-PD-1 (aPD1) in a sustained manner. Anti-PD-1 and glucose oxidase-loaded pH-touchy dextran nanoparticles had been delivered through MN [78]. A topical cream containing five-fluorouracil is used to deal with basal cell carcinoma. The permeability of 5-fluorouracil turned into improved up to 4.5 instances whilst the cream becomes implemented on the pores and skin treated with stable MNs. Significant inhibition of tumor increase in addition confirmed improved efficacy the use of Microneedles [79]. Bhatnagar et al. investigated the shipping of chemotherapeutic retailers- tamoxifen and gemcitabine through MNs for the remedy of most breast cancers. Localized delivery of those pills might help to reduce the facet consequences [80]. Polymeric MNs were also investigated for skin cancer and localized delivery of anticancer capsules [81]. In **Table 2** we've mentioned MNs applied in most cancers therapy [82-88].

MNs in Diabetes

Yu et al. established that glucose-responsive MN array patches regulated the glucose successfully in blood employing turning in insulin for type 1

Table 2. Application of MNs in Cancer Treatment

Drug used	Type of study	Results	Reference
Doxorubicin and docetaxel	*In vivo*	Increased mice survival and impaired tumor growth	[80]
5-Aminolevulinic acid	*In vivo*	Reduction of the tumor volume in 56%	[82]
Doxorubicin	Proof-of concept	Increased doxorubicin delivery across the skin	[83]
Lipid-coated cisplatin nanoparticles	*In vivo*	Stalled tumor progression and increased skin safety	[84]
Gold nano cubes and doxorubicin	*In vivo*	Increased mice survival and impaired tumor growth	[85]
5-Aminolevulinic acid	*In vivo*	Reduction of the tumor volume in 70%	[86]
Doxorubicin and LaB6 nano materials	In vivo	Complete eradication of the tumor and increased mice survival	[87]
5-aminolevulinic acid	Proof-of concept	Increased the drug penetration in 2- fold	[88]

Table 3. Examples of marketed MNs-based products

Name of product	Company	Description	Use
Dermaroller®	Dermaroller® Germany, White Lotus	A cylindrical roller with solid or metal micro-needles, 0.2–2.5mm in length.	Enhance skin texture, treat scars and hyper pigmentation
C-8 (Cosmetic type)	The Dermaroller Series by Anastassakis K	A needle length of only 0.13mm (130 μm)	Used to improve penetration of topical agents
CIT-8 (Collagen Induction Therapy)	The Dermaroller Series by Anastassakis K.	A needle length of 0.5mm (500 μm)	Used in collagen induction and skin remodeling.
MF-8 type	The Dermaroller Series by Anastassakis K.	A needle length of 1.5mm (1500 μm)	Treat scars.
MS-4	The Dermaroller Series by Anastassakis K	A Small cylinder, 1 cm length, 2 cm diameter, and 4 circulars arrays of needles which are 1.5mm in length	Used on facial acne scars
Micro Hyala®	CosMed transdermal drug delivery	Dissolving micro-needle patch with hyaluronic acid	Wrinkle treatment
Lite Clear®	Nano-med skincare	Solid silicon micro-needles are used as pre-treatment and then drug applied topically.	Treats acne and skin blemishes
Soluvia®	Sanofi Pasteur Europe	Hollow micro-needle attached to a syringe	Influenza vaccination
h-patch	Valeritas	Small adhesive machine-like patch is used	To deliver drugs in subcutaneous tissue (insulin)

diabetes remedy [89]. Chen et al. developed a smart and pH-responsive MN patch primarily based on alginate for type 2 diabetes therapies [90]. Lee et al. developed a portable electrochemical tool that monitors pH, temperature, humidity, and the level of glucose timely in sweat yet also be actuated thermally to launch metformin transcutaneously for diabetes remedy [91].

Accepted MNs based products

The first MN-based formulation was the derma roller. Several MN-based products are available in the market which is used in medical and cosmetic purpose [92]. Captivatingly, MNs present important qualities rather than conventionally applied medication in transportation to the targeted site or systemic delivery. Hence, there had been a high expansion in scientific and industrial movement in this field from the earlier period. Some of them are described in **Table 3**. Many development companies from Germany, US, Europe, Japan are selling various MNs based formulations [93].

Associated Patents

From the previous decades, MNs were extensively used as potential release carriers. In this respect, the

Table 4. Micro-needle associated patents in pharmaceutical field

Conditions or diseases	Patent number	Description
Electrochemical biosensing in body fluid	13/2019 201811044930	In this invention, it has developed a modern method for MNs that prints assembled screens. Electrode fixes the bio-sensing electrode to print the screen that sensing of blood glucose, cholesterol HbA1C and like.
Treatment of hyperkeratosis, injury, and pain in conditions like warts, corns, calluses, acne, psoriasis, keloids, microtrauma, eczema	48/2018 201721017985	The MNs patches based topical drug delivery system incorporated with keratolytic agents. The patch comprises micron-scale protrusions that penetrate via the SC and delivers the active pharmaceutical ingredient across the SC to improve the permeation of drugs. A keratolytic agent reduces the intercellular cohesiveness of the horny cells and thus enables speedy shedding of keratinized cells [70].
Management of anxiety	42/2018 2017201721013027	In this patent novel, the buspirone microemulsion method has developed using the phase titration method and tested for its efficiency in the skin. It enhances transdermal delivery.
Enhancement of immunogenicity	WO/2010/01360	It has enhanced immunogenicity using an MNs for the Japanese encephalitis virus antigen derived from kidney cells of monkey and concluded that antibody against a Japanese encephalitis virus antigen has efficiently enhanced.
Enhancing the immunogenicity against influenza virus	WO/2010/001671	Polylactic acid-coated MNs of an influenza vaccine that is the H1N1 strain, H3N2 and types B strain, and brought into direct skin contact that enhances immunogenicity against influenza virus.
To treat pimples, stains, or wrinkles	20150290163	MNs contain a substrate, water-swelling polymer, and retinoic acid. It dissolves in an enormous amount of water.
Local anaesthesia	20200170940	The invention provides immediate acting local anesthetic MNs easily applied to the oral cavity or site, In which a needle part dissolves in a mucous membrane when applying to an oral mucous membrane or gums.
Botulinum toxin to treat diseases	20170209553	To treat disease, disorder, or condition therapeutic amount of toxin was added to the MN array [71].
Diagnosis of allergy	20100030100	This is an invention of a diagnostic MN device for the detection of an allergy. It holds at least one allergen that enables to perform skin tests with an effortless process in the diagnosis of allergies. These MNs have been prepared using non-metallic synthetic or natural resin material.

Table 5. Associated MNs under clinical trials

Study Title	Interventions	Conditions	Status
MNs patch study in healthy infants/young children	MNs Formulation 1 and 2	Vaccination Skin absorption	Completed 2020
Pain and safety of MNs in the oral cavity	MNs	Oral cavity disease	Completed 2019
Minimally invasive sensing of beta-lactam antibiotics	Phenoxymethyl Penicillin, MNs	Healthy volunteers	Completed 2019
Comparison of 1,550-nm laser and fractional radiofrequency MNs for the treatment of acne scars in ethnic skin	Fraxel Restore and Fractora	Acne scars	Completed 2019
Analysis of noninvasively collected MN device samples from mild plaque psoriasis for use in transcriptomics profiling	MN device	Psoriasis vulgaris	Completed 2019
Safety study of suprachoroidal triamcinolone acetonide via MN to treat uveitis	Triamcinolone , acetonide	Uveitis, intermediate, uveitis, posterior uveitis	Completed 2019
A study of the use of MN patches to deliver topical lidocaine in the oral cavity	MNs Patch	Topical anesthesia	Completed 2019
The use of MNs to expedite treatment time in photodynamic therapy	MN roller	Keratosis, actinic	Completed 2019
A study to evaluate the long-term safety of M207 in the acute treatment of migraine	M207 MNs System	Migraine	Completed 2019
Safety and efficacy of ZP-zolmitriptan intracutaneous MN systems for the acute treatment of migraine	ZP-Zolmitriptan	Acute migraine	Completed 2018
Clinical evaluation of healthy subjects receiving intradermal saline using the MN adapter (Model UAR-2S)	MNs Adapter (Model UAR-2S	Intradermal injection	Completed 2018
The effect of MN pretreatment on topical anesthesia	Device: Sham MNs Roller Device: MNs Roller	Pain	Completed 2018
A split-mouth trial to compare MNs vs. standard needles in dental anesthetic delivery	MNs Device	Dental pain Anesthesia	Completed 2018
Glucose measurement using MN patches	MNs patch	Diabetes	Completed 2018
The use of MNs with topical botulinum toxin for the treatment of palmar hyperhidrosis	Device: MNs Device: Sham MNs	Hyperhidrosis	Completed 2017
The use of MNs in photodynamic therapy	MNs	Actinic keratosis	Completed 2017
Insulin delivery using MNs in type 1 diabetes	MNs	Type 1 diabetes mellitus	Completed 2014
A study to assess the safety and efficacy of an MNs device for local anesthesia	Micron Jet	Local anesthesia Intradermal injections	Completed 2013
Optimization of tuberculosis intradermal skin test	MNs BD 1.5 mm 30G	MNs BD 1.5 mm 30G	Completed 2013
Pilocarpine Micro needles for Sweat Induction (PMN-SI)	MNs patch	Cyclic fibrosis	Not yet recruiting
MNs for Diagnosis of LTBI	Diagnostic Test: TST vs PPD microneedle test	Tuberculosis	Not yet recruiting

researcher gives much more concentration to the survey to progress the MNs material and its properties. Thus, it can be proficiently used for the effectual delivery of therapeutics with low side effects. Several patents related to MNs are present in the drug delivery system. The inventive approach for targeted drug delivery of active agent through MNs associated patents are showed in **Table 4**.

Clinical trials

Various clinical trials were conducted on MNs and resulted in an efficient role in many respective though a limited number has been accepted for human subjects. Kaushik et al. conducted the first research on MNs in human subjects in the year 2001. The motto was to check whether the silicon MNs can avoid pain compared to a 26-gauge hypodermic needle or not. The result showed that the pain developed by the MNs was lower than that of hypodermic needles [94]. Arya and his teammates also did research to evaluate whether MNs cause local skin irritation or not. The study was conducted among 15 human volunteers and found micro needles did not cause any swelling, pain, or erythema at the site of application of the patch. The patients were able to self-administer the patches without difficulty [95]. An open trial was conducted among 10 patients for hyaluronic acid-based MN patches to evaluate the therapeutic efficacy against psoriasis. Calcipotriol-betamethasone ointment was useful on the skin. MN patch is used once a day for a week. The result showed a considerable decrease in the psoriatic plaques and thus concluded MNs are a better option than conventional cream applications [96]. This promising method is flexible enough and can be used to deliver proteins up to 100 mg that can go straight into the blood circulation [97]. In **Table 5** the MNs under clinical trials has been described [98]

Conclusion

Even though multiple drug delivery systems have been designed for targeted delivery, MNs are still unique due to their multipurpose advantages. The transportation of bio-actives by using MNs has shown the revolutionary window for life-threatening illnesses. The MNs have already been confirmed to be a more effective and safe method of drug delivery systems. Overall, the application of MNs becomes more famous, and a large number of research works is going. Several research and literatures have described the significance of MNs in the case of drug delivery via a different route of administration. Still, there is a need for more research about MNs for future multipurpose use in pharmacy.

Conflict of Interest

All the authors declare no conflict of interest.

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